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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,522	04/13/2006	Alexander Steinkasserer	106985-4	8817

27384 7590 07/20/2010

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EXAMINER	
JUEDES, AMY E	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
07/20/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,522	STEINKASSERER ET AL.	
	Examiner	Art Unit	
	AMY E. JUEDES	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29,31-33,35-39,46,49,51 and 53-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,31-33,35-37,46,49,51,53 and 54* is/are rejected.

7)☒ Claim(s) *38,39 and 55* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/26/10, 2/10/10, 4/27/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks, filed 4/27/10, are acknowledged.
Claims 30 and 50 have been cancelled.
Claims 29, 32-33, 35, 37-38, 49, and 53 have been amended.
Claims 54-55 have been added.
Claims 29, 31-33, 35-39, 46, 49, 51, and 53-55 are pending and are under examination.

2. The information disclosure statement filed 4/27/10 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because The information disclosure statement has not considered because it has been filed after first action, but no statement as specified in 37 CFR 1.97(e) or fee set forth in 37 CFR 1.17(p) has been provided. It has been placed in the application file, but the information referred to therein has not been considered. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

3. The oath or declaration stands objected to. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.
The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

4. Claim 53 is objected to because of the following informalities: The claim recites that the protein is selected "from the group consisting of", but recites only a single

sequence. Amendment to the claim to read "A monomeric soluble form of a member of the CD83 family of proteins (monomeric CD83 protein) consisting of amino acid residues 1 to 130 of SEQ ID NO: 8..." would be remedial, and would place claim 53 in condition for allowance.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 29, 31-33, 35-36, 46, 49, and 51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A monomeric soluble form of CD83 consisting of amino acid residues 20 to 144/145 of SEQ ID NO: 2, or consisting of amino acid residues 1 to 129/130 of SEQ ID NO: 8, wherein the third or fifth cysteine residue is substituted, and a method of treating multiple sclerosis, tissue or organ transplant, chronic inflammatory bowel disease, Morbus Crohn, Colitis ulcerosas, and IDDM comprising administering said monomeric soluble form of CD83

does not reasonably provide enablement for:

A monomeric soluble form of CD83 consisting of amino acid residues 20 to 144/145 of SEQ ID NO: 2 or consisting of amino acid residues 1 to 129/130 of SEQ ID NO: 8, wherein the one or more cysteine residues are substituted, and a method for treating or preventing a disease with said monomeric soluble form of CD83.

As set forth previously, The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, *in re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

"The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ

18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)" The MPEP further states that physiological activity can be considered inherently unpredictable.

The specification provides insufficient guidance to enable one skilled in the art to make and use the soluble CD83 proteins as broadly claimed. The instant claims are drawn to a soluble CD83 protein consisting of amino acid residues 20 to 145 of SEQ ID NO: 2 or residues 1 to 130 of SEQ ID NO: 8, wherein or more cysteine residues are substituted. It is noted that the claims do not specify any functional requirement of the claimed CD83 polypeptides. The recited sequences comprise 5 cysteine residues. The instant claims encompass proteins comprising mutations of up to all 5 cysteine residues. Cysteine residues play an important role in the structure and function of proteins, and many proteins simply cannot form stable native structures without a disulphide bond between cysteine residues (see Thangudu et al., 2007). Furthermore, it is known that even a single cysteine substitution can dramatically effect the function of proteins (See Zhong et al., 2006). The instant specification on page 21-22 discloses that the monomeric soluble CD83 proteins of the invention are useful for binding and causing disruption in the binding of dendritic cells to T cells, particularly in pharmaceutical formulations. However, given the importance of cysteine residues in the structure and function of proteins, it would be extremely unpredictable as to whether even a single cysteine substitution (much less more than one) would result in a protein with the same structure and function of wild type CD83 protein. The instant specification demonstrates that a CD83 protein consisting of residues 20 to 145 of SEQ ID NO: 2, wherein a single cysteine at position 129 has been substituted with another amino acid residue functions to inhibit dendritic cell/T cell interaction. SEQ ID NO: 8 of the instant application represents the sequence of residues 20 to 145 of SEQ ID NO: 2, including a peptide linker at the N-terminus. Thus, the specification demonstrates that substation of the fifth cysteine residue of amino acids 20 to 145 of SEQ ID NO: 2 or residues 1 to 130 of SEQ ID NO: 8 (i.e. residues 129 and 114, respectively) results in a functional protein. However, the specification does not provide any guidance as to the overall structure of CD83, including the presence of cysteine disulphide bonds that might be critical for structure/function. Furthermore, the instant specification does not provide any guidance regarding the use of other CD83 proteins in which up to all 5 cysteine residues have been substituted. Said CD83 proteins would not likely share the same structure as the CD83 of SEQ ID NO: 2, nor would they likely be capable of binding and disrupting dendritic cell/T cell interactions. Thus, given the breadth of the claims, the unpredictability of the art, and the lack of guidance by the instant specification, one skilled in the art would not be able to make and use the CD83 proteins as broadly claimed.

Furthermore, claims 49-51 are drawn to methods of treatment employing the monomeric CD83 proteins. As noted above, it would be extremely unpredictable as to whether any cysteine substitution, including multiple cysteine substitutions, would result in a functional CD83 protein. Therefore, for the same reasons set forth above, it would require undue experimentation to use the monomeric CD83 proteins, as broadly claimed in claim 29, for treatment methods which would require a structurally and functionally intact soluble protein. Additionally, the instant claims encompass not only treatment, but prevention of disease. Given its broadest reasonable interpretation, the term prevention encompasses a complete prevention such that no signs or symptoms of disease ever develop. Thus,

based on the unpredictability of the art and the breadth of the claims, the instant specification must provide a sufficient an enabling disclosure commensurate in scope with the instant claims. The instant specification demonstrates that soluble CD83 is effective for treating, but not completely preventing EAE, an art recognized animal model of multiple sclerosis. However, this is not commensurate in scope with the instant claims. Thus, given the breadth of the claims, the unpredictability of the art, and the lack of guidance provided by the instant specification, it would require undue experimentation to practice the claimed invention.

Applicant's arguments and the declaration of Dr. Charles Nicolette have been fully considered, but they are not persuasive.

The Nicolette declaration demonstrates that soluble CD83 proteins in which the third or fifth cysteine residue have been mutated are effective in treating animal models of graft rejection, IDDM, and colitis. Applicant concludes that the declaration provides evidence that substitution at other than the firth cysteine residue is operable.

The declaration provides evidence that substitution of the third or fifth cysteine residue results in a functional soluble CD83 molecule, and that said CD83 molecules are effective in treating graft rejection, IDDM and colitis. However, claim 29 still encompass a soluble monomeric CD83 protein in which more than one cysteine residues is substituted. In fact, the claims encompass proteins in which all 5 cysteine residues might be substituted. As noted above, the effect of cysteine residue substitution is highly unpredictable. While the declaration demonstrates substitution of the third OR fifth cysteine residue can result in a functional protein, this is not commensurate in scope with the instant claims which encompass proteins containing up to five cysteine substitutions. Additionally, even when the claims are limited to a single cysteine substitution (i.e. claim 36), given the unpredictably of the art, the fact that a certain cysteine residue substitution is tolerated, does not provide any predictive information as to the structure/function of proteins in which other cysteine residues are substituted. In fact, WO 2009/142759 submitted as a reference on Applicant's IDS filed on 2/10/10 under 37 CFR 1.97 with the fee set forth in 37 CFR 1.17(p) demonstrates the unpredictability of cysteine substitution of CD83. WO 2009/142759 teaches that substitution of cysteine 2 alone or with one or more other cysteine residues, results in a significant change in CD83 protein structure, suggesting that an intramolecular disulphide bond at cysteine 2 may be important in stabilizing protein structure (see page

47-48, in particular). Thus, based on the teachings of WO 2009/142759, the use a potentially nonfunctional, structurally altered CD83 protein with one or more cysteine residue substitutions including cysteine 2, would be highly unpredictable. Furthermore, Applicant has not provided any evidence that that multiple cysteine residue substitution, as encompassed by the instant claims, is routine and predictable and expected to result in a functional protein that could be made and used by one of skill in the art. Additionally, the specification does not provide any guidance as to the overall structure of CD83, including the nature of the cysteine disulphide bonds that would be critical for structure/function. Furthermore, the instant claims encompass using said CD83 proteins with more than one cysteine residue substitution in treatment of disease. Given the unpredictability and potentially nonfunctional nature of cysteine substituted proteins, it would require undue experimentation to treat disease with the CD83 proteins as broadly claimed. Furthermore, the instant claims encompass preventing disease, which as noted in the original rejection is highly unpredictable. The declaration provides evidence of treatment, but not a complete prevention of disease, as is encompassed by the instant claims.

7. No claim is allowed. Claims 37-39 and 54-55 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

8. **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later

than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, whose telephone number is 571-272-4471. The examiner can normally be reached on 8am to 4:30pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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